REMARKS

Status of the Claims

Claims 2-7, 22-25, 29-36, 43-52, and 58-64 were previously canceled, without prejudice. In the Final Office Action, Claims 16, 17, 19, 20, and 41 were withdrawn from consideration and Claims 1, 8-15, 18, 21, 26-28, 37-40, 42, 53-57, and 65-72 were rejected. In the amendment presented herewith, Claims 1, 8, 11-15, 26-28, 41, 42, 65, 66, and 68-72 have been amended and Claims 16, 17, 20, 21, 53-57, and 67 have been canceled, without prejudice. Claims 1, 8-15, 18, 19, 26-28, 37-42, 65, 66, and 68-72 are now pending; although, Claims 19 and 41 are still withdrawn from consideration.

Amendments to the Claims

Claim 1 has been amended for clarity by reciting a method for inhibiting "reseeding of cancer cells during or after surgical resection of a tumor." Support for this language can be found in the as-filed specification at page 16, lines 7-8, where it states that the compounds can be used to inhibit the "reseeding that can occur during or after surgical resection of a tumor."

Claim 1 has been further amended to recite that the administration of the compound "is within 10 days of the resection." Support for this language can be found in Claim 67, which is redundant a result of this amendment to Claim 1 and has therefore been canceled herein. It would be understood that administration "within 10 days of the resection" includes administrations of the compound that are within 10 days prior to resection as well as administrations of the compound that are within 10 days after the resection, or both. This would be understood because the specification at page 16, lines 9-10, states that when administering the compound "**prior to or after** the resection, the transiently suspended cells can be efficiently caused to apoptos" (emphasis added). Further, at page 16, lines 13-16, it states that the compound is "administered **prior** to the resection or **after** the resection or **both**" (emphasis added). Thus, the phrase "within 10 days *of* the resection," and the similar phrases in dependant Claims 68-72, would be understood to include administrations that occur within the recited period before the resection, within the recited period after the resection, or within the recited period both before and after the resection.

Also, Claim 1 has been amended for clarity. Specifically, the phrase "the NF-κB inhibitor" is simply replaced by the phrase "the compound." As a result of this amendment,

dependant Claims 26-28, 41, 42, 65, 66, and 68-72 have been amended for antecendency and thus they likewise use the phrase "the compound."

Other amendments have been made to simply correct spelling and tenses.

No new matter has been added by these amendments; therefore, examination is requested on the claims as amended herewith.

Interview Summary:

The undersigned attorney and inventor, Dr. Scott Kuwada, would like to express their thanks for the courtesies shown by Examiners Pagonakis and Fetterolf during the interview of December 8, 2009.

During the interview, Dr. Kuwada went through a presentation describing his research, the invention, and some relevant data. Afterwards, various claim language were discussed in light of the presentation and the pending rejections. While the allowability of particular claim language was not expressly discussed, the amendments to the claims herein are made in an effort to comport with the Examiners' comments and suggestions made in the interview. It is believed that the claims are now in a form that is acceptable to the Examiners.

Also, Examiner Pagonakis suggested that Dr. Kuwada present a Declaration discussing data involving the activity of other NF-κB inhibitors as well as assays of COX inhibition. Such a Declaration is provided herewith under 37 C.F.R. § 1.132.

Response to Rejection under 35 U.S.C. § 112, 2¶

The Final Office Action rejected Claims 1, 65, and 67-72 under 35 U.S.C. § 112, 2 ¶, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Specifically, the Examiner contended that Claims 65 and 67-72 were unclear in view of base Claim 1, which recited that an inhibitor is administered to a subject that "has had" a tumor resected. This rejection is believed to be rendered moot by the amendments to the claims presented herewith and discussed above.

Response to Rejections under 35 U.S.C. § 103

The Examiner maintained the Rejection of under 35 U.S.C. § 103, alleging that Claims 1, 8-15, 18, 21, 26-28, 37-40, 42, 53-57, and 64-72 are obvious over Izban *et al.* (Human Pathology 31(12):1482-1490, 2000) in view of Kahn *et al.* (US Patent 7,175,679). In view of the cancellation of various claims, this rejection now applies to Claims 1, 8-15, 18, 26-28, 37-40, 42, and 67-72.

It is believed that in view of the issues discussed in the interview, and the claim amendments presented herewith, the current obviousness rejection has been overcome. Specifically, the claims now recite a method for inhibiting "reseeding of cancer cells during or after surgical resection of a tumor." As noted in the specification at page 1, lines 21-22, tumor resection can result in iatrogenic seeding of cancer cells. In other words, tumor resection surgery can free tumor cells from their matrix, and after being transiently detached, some can readhere to various tissues and grow, resulting in additional tumors in the patient. In fact, it is estimated that this unwanted, and often deadly consequence, occurs in 50% of abdominal resections. So the goal of helping the patient by surgically removing the tumor can, in some instances, work to actually spread the tumor to other locations.

It has been found that the readhesion of cancer cells following a period of transient suspension (such as would occur during a reseeding event caused by surgery) causes a large activation of NF-κB—much larger than the normally heightened NF-κB activity seen in many cancers. This heightened activation renders the cancer cells exquisitely sensitive to NF-κB inhibition-induced apoptosis (*see e.g.*, page 7, lines 27-30). *See also* Figure 4A of the application, which was discussed in the interview. Treating adherent cells with a NF-κB inhibitor BAY-11-7085 produced an unremarkable effect (about 20% induction of apoptosis at 100 μM). However, when the cancer cells were transiently suspended and then allowed to adhere, a remarkable and significant result was observed (about 80% induction at 20 μM). It is also significant to point out that the large activation of NF-κB following readhesion was relatively short lived. *See* Figure 4C, which was also discussed in the interview. There was a large amount of nuclear NF-κB at 1 hour; but it diminished to a relatively normal amount at 24 hours. Thus, the window of opportunity to induce apoptosis in readhering cancer cells and thereby inhibit reseeding is short.

In light of the above, none of the cited references disclose or otherwise teach targeting NF-κB (let alone any other target) to inhibit the iatrogenic reseeding of cancer cells. At best, the cited references only generally teach the use of NF-κB as a suitable target for treating various cancers. Following such a general teaching, one could merely expect the result shown in Figure 4A where adherent cancer cells treated with BAY-11-7085 resulted in some, albeit unimpressive, induction of apoptosis. In contrast, inhibiting the reseeding of cancer cells after transient suspension (*i.e.*, the other curve in Figure 4A) is highly effective and is nowhere mentioned or

suggested in the cited references. Because NF-κB is not acknowledged as being a useful or sensitive target for cancer cells during the particular event of reseeding, the inhibition of cancer cells at this critical time by inhibition of NF-κB is not obvious in view of the cited reference.

Moreover, it has been found that not all NF-κB inhibitors will work for the indication recited in the present claims. So assuming, *arguendo*, the skilled artisan were to seek out NF-κB as a target for inhibiting reseeding of cancer cells, there is nothing in the cited references that would point to using the particular compounds recited in the claims (as opposed to some other NF- κB inhibitors). Indeed, there is much more to the inventor's discovery than simply using a NF-κB inhibitor to treat cancer. Only certain compounds are effective at inducing apoptosis at the reseeding event. Enclosed herewith is the Declaration of Dr. Scott Kuwada, which shows various known NF-κB inhibitors that did **not** produce the pro-apoptotic effect in reseeding cancer cells seen with the compounds recited in the amended claims. So while NF-κB inhibition is involved, there are other mechanisms at work as well. The particular mechanism believed to be at work, which is actually the convergence of several pathways, was discussed in the interview.

Lastly, the Final Office Action maintained that because COX-2 is overexpressed in colorectal tumors, and that NF-κB is known to regulate COX-2, NF-κB would be a suitable target for colorectal tumors. While NF-κB (and COX-2) may very well be a suitable target for **attached** colorectal tumors, this says nothing about inhibiting the reseeding of cells after being transiently detached (again *see* Figure 4A). It also says nothing about which compounds might be used to inhibit reseeding (as noted above not all NF-κB inhibitors would work). Moreover, the recited compounds do not to even inhibit COX-2. So the logic that one would use the recited compounds to treat colorectal tumors because they would inhibit COX-2 is false.

In summary, the event of reseeding creates a significant, and short lived, target for inducing apoptosis of cancer cells left behind from a surgical resection. This event involves NF-κB, as well as other mechanisms. As such, the methods require certain compounds to be administered at times close to the reseeding event. Therefore, the claims are not directed to merely treating cancer cells, they are directed to inhibiting the reseeding of cancer cells at a particularly critical period of time with certain compounds. Such claims are nowhere suggested or gleaned from the cited references and are therefore patentable.

CONCLUSION

In light of the amendments and arguments presented herein all of the rejections are believed to be overcome. As such, Applicants respectfully request notification of same. The Examiner is encouraged to contact the undersigned if it may advance prosecution.

Enclosed herewith is payment in the amount of $960.00, which includes the $555.00 fee under 37.C.F.R. §1.17(a)(3) for the Three-Month Extension of Time and the $405.00 fee required under 37 C.F.R. § 1.17(e) for the Request for Continued Examination. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence – including any items indicated as attached, enclosed, or included – is being transmitted by EFS-WEB on the date indicated below.

/Christopher L. Curfman/ — December 24, 2009

Christopher L. Curfman — Date